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Supplemental Material

Colorectal Cancer and Long-Term Exposure to Trihalomethanes in Drinking Water: A Multicenter Case-Control Study in Spain and Italy

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Figure S1. Distribution of exposure density of average lifetime THM concentrations in residential tap water (μg/l) among 1837 cases and 3488 controls with exposure estimates ≥70% of the exposure window. Note that scale of x- and y-axes differ by area.

Figure S2. Exposure-response relationship between residential trihalomethane (THM) levels (X axis, in μg/l) and colorectal cancer risk (Y axis, expressed in odds ratios) among 1837 cases and 3454 controls. Odds ratios (95 CI) are adjusted for sex, age, area, education, smoking, physical activity, non-steroidal anti inflammatory drugs and family history of colorectal cancer. Excludes unsatisfactory questionnaires and subjects with THM estimated less than 70% from the exposure window. Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals.

Figure S3. Spline of colorectal cancer risk (odds ratio, Y axis) associated with chloroform levels (μg/l, X axis) among men, from generalized additive models adjusted for age, sex, education, smoking, non-steroidal anti inflammatory drugs, smoking, physical activity and family history of colorectal cancer. P-value of gain from the linearity is statistically significant in Barcelona (p-value <0.001), Leon (p-value 0.03), Madrid (p-value 0.04), and Navarra (p-value 0.01). Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x -axes differ by area.

Figure S4. Spline of colorectal cancer risk (odds ratio, Y axis) associated with total brominated THM levels (μg/l, X axis) among men, from generalized additive models adjusted for age, sex, education, smoking, non-steroidal anti inflammatory drugs, smoking, physical activity and family history of colorectal cancer. P-value of gain from the linearity is statistically significant in Barcelona (p-value <0.001), Cantabria (p-value <0.01), and Navarra (p-value <0.01). Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x-axes differ by area.

Figure S5. Exposure-response relationship between ingested THM levels (X axis) and colorectal cancer (Y axis, expressed in odds ratios (OR) with 95% confidence intervals (95% CI)) among 2047 cases and 3684 controls. Adjusted for sex, age, area, education, smoking, physical activity, non-steroidal anti inflammatory drugs, and family history of cancer. Excludes unsatisfactory interviews and subjects with less than 70% THM estimated from the exposure window. P-value gain compared to linearity is <0.01 for all models, expect for chloroform in women (p-value=0.32). Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals.Note that scale of x-axes differ by area.

Figure S6. Exposure-response relationship between shower-bath THM levels (X axis) and colorectal cancer risk (Y axis, expressed in odds ratios (OR) with 95% confidence intervals (95% CI)) among 1702 cases and 3269 controls. Adjusted for (sex), age, geographical area, education, non steroidal anti inflammatory drugs consumption, smoking, physical activity and family history of colorectal cancer Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x-axes differ by area.

Table S3. Association between colorectal cancer and average THM concentrations in residential tap water by cancer site among 1273 colon cases, 537 rectal cases, and 3454 controls (27 cases had an unspecified localization).